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1. Untranslatable words are replaced with asterisks (\*\*\*)
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## **CLAIM + DETAILED DESCRIPTION**

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**[Claim(s)]**

**[Claim 1]** Skin external preparations which contain two or more sorts of film formation agent 1-5 weight %, 1 to 10 weight % of water, 2.2 to 25 weight % of plasticizers, 0.1 to 5 weight % of antifungals, and 50 to 95 weight % of alcohol, and are characterized by the rates to the film formation agent of plasticizers being 2.2-5 in a bulk density.

**[Claim 2]** The above-mentioned film formation agent The ethylcellulose, polyvinyl butyrate, hydroxypropylcellulose phthalate, A methacrylic acid methacrylic acid methyl copolymer, a methacrylic acid diethylaminoethyl methacrylic acid methyl copolymer, A methacrylic acid ethyl methacrylic acid chlorination trimethylammonium ethyl copolymer, A methacrylic acid methyl methacrylic acid butyl methacrylic acid diethylaminoethyl copolymer, Skin external preparations according to claim 1 which are two or more sorts chosen from a methacrylic acid ethyl acrylate copolymer, an ethyl

acrylate methacrylic acid methyl methacrylic acid chlorination trimethylammonium ethyl copolymer, and a methacrylic acid methylacrylic acid ethyl copolymer.

[Claim 3] Skin external preparations according to claim 1 which are one sort as which the above-mentioned plasticizers are chosen from adipic acid diisopropyl, the sebacic acid diethyl, diethyl phthalate, glyceryl mono-olate, and triethyl citrate, or two sorts or more.

[Claim 4] The above-mentioned antifungal Clotrimazole, miconazole nitrate, econazole nitrate, Skin external preparations according to claim 1 which are one sort chosen from isoconazole nitrate, a pyrrole nit phosphorus, the tolnaftate, BIFUMASHIN, a trichomycin, a cyclo PIROKUSUOKU lamin, exalamide, and the haloprogin, or two sorts or more.

[Claim 5] Skin external preparations according to claim 1 whose above-mentioned alcohol is ethanol and/or isopropanol.

[Claim 6] As the above-mentioned film formation agent, 1 to 4 weight % of ethylcellulose, and 0.1 to 1 weight % of methacrylic acid methacrylic acid methyl copolymers, 1 to 10 weight % of water, 2.5 to 25 weight % of plasticizers, skin external preparations according to claim 1 that contain 50 to 95 weight % of ethanol as the above-mentioned antifungal as 0.1 to 2 weight % of clotrimazole, and the above-mentioned alcohol.

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#### [Detailed Description of the Invention]

##### [0001]

[Industrial Application] This invention relates to the still more detailed skin external

preparations for dermatomycosis treatment about skin external preparations.

[0002]

[Description of the Prior Art] It is said that the dermatomycosis represented by athlete's foot has many disease persons, and is the big social problem which hid since it was moreover hard to recover. It is said that it is [ that this illness cannot recover easily ] reasonable in a medicine not storing in a horny layer but being hard to demonstrate the curative effect of a medicine since it passes through a horny layer immediately and shifts into blood even if a medicine does not permeate easily and permeates, since a disease germ's existence place is in a horny layer. Many people have succeeded in the trial which raises the drug level in a horny layer on the basis of this situation. For example, the thing for which a medicine is dissolved in a medicine and the good dissolution medium of compatibility, By promoting osmosis into the skin of a medicine, heightening the effect that a medicine permeates the skin by blockading the skin using blockade equipments, such as plaster, or blending a film formation agent with a medicine, and making the film having contained the medicine form on the skin It has succeeded in the trial which raises osmosis into the skin of a medicine.

[0003] since [ however, ] the crystal of a medicine will deposit soon if a medicine and the good dissolution medium of compatibility are boiled occasionally, and it carries out, and volatility is high, therefore applies the tablet containing this to the skin, It is easy to trigger the skin reaction which is not desirable as for the rash of the skin by an adhesive etc. and is not practical, when the absorptivity of a medicine is barred on the contrary, or the blockade with blockade equipments is made and a using feeling will be spoiled remarkably. since [ moreover, / in which a film dissipates easily by sweat etc. in the

tablet which blended the film formation agent when a film formation agent is water solubility, and a no-water solubility film formation agent is alike occasionally, and carries out when a film formation agent is no-water solubility / that stiffness is high ] it is weak, It was in the trend in which a film breaks and a medicine tends to carry out exfoliation defluxion from the skin, and there was a big problem about the improvement of the reservoir in the horny layer of a medicine.

[0004]

[Problem(s) to be Solved by the Invention] Therefore, the purpose of this invention is to offer the skin external preparations for skin fungus treatment which may make an antifungal store in a horny layer efficiently.

[0005]

[Means for Solving the Problem] The result for which examination was wholeheartedly repeated in view of this actual condition about the tablet with which this invention persons may make an antifungal store in a horny layer, It found out that the tablet excellent in the operation which is excellent in pliability and makes a medicine permeate in obstructiveness and a horny layer by blending plasticizers was obtained so that two or more kinds of film formation agents might be blended and the rate to the film formation agent of plasticizers might be set to 2.2-5 by a bulk density, and invention was completed.

[0006] This invention Namely, two or more sorts of film formation agent 1-5 weight %, 1 to 10 weight % of water, The skin external preparations which contain 2.2 to 25 weight % of plasticizers, 0.1 to 5 weight % of antifungals, and 50 to 95 weight % of alcohol, and are characterized by the rates to the film formation agent of plasticizers being 2.2-5 in a

bulk density are offered.

[0007] [ here ] as a film formation agent used by this invention Especially if it is a water-soluble low film formation agent, will not be limited, but The ethylcellulose, Polyvinyl butyrate, hydroxypropylcellulose phthalate, A methacrylic acid methacrylic acid methyl copolymer, a methacrylic acid diethylaminoethyl methacrylic acid methyl copolymer, A methacrylic acid ethyl methacrylic acid chlorination trimethylammonium ethyl copolymer, A methacrylic acid methyl methacrylic acid butyl methacrylic acid diethylaminoethyl copolymer, It is desirable to use two or more sorts chosen from a methacrylic acid ethyl acrylate copolymer, an ethyl acrylate methacrylic acid methyl methacrylic acid chlorination trimethylammonium ethyl copolymer, and a methacrylic acid methylacrylic acid ethyl copolymer. In this invention, it is required to use it, combining these film formation agents two or more sorts. Since the film formed breaks easily firmly when one sort of film formation agents are used, the Reason breaks, and drops out of the skin, but it is because the stiffness of a film is controlled and defluxion can be prevented, if it uses combining two or more sorts. As a combination of these film formation agents, combination with celluloses, such as ethylcellulose, and copolymers, such as a methacrylic-acid methacrylate copolymer, a methacrylate copolymer, and a methacrylic-acid acrylate copolymer, is desirable. The most desirable combination among these film formation agents is the ethylcellulose and a methacrylic acid methacrylic acid methyl copolymer.

[0008] Especially the loadings of these films formation agent have the desirable thing of the skin external-preparations whole quantity considered as 3.5 to 4.5% one to 5 weight % (% only shows hereafter). Since about [ that obstructiveness does not change ] or a coat

becomes thick too much even if the film plasticity of loadings exceeds 5% rather than they are [ and ] enough at less than 1%, the applied tablet is easily omitted from the skin.

[0009] Furthermore, in the combination of the ethylcellulose and a methacrylic acid methacrylic acid methyl copolymer, it is desirable to set the bulk density of these two film formation agents to 5:1-8:1. By blending a film formation agent by this bulk density, when it applies to the skin, the skin external preparations which form the film with moderate stiffness and pliability which does not exfoliate easily can be obtained.

[0010] The water blended with the skin external preparations of this invention has the operation which dissolves two or more sorts of film formation agents, and is an indispensable element in this invention. In order to demonstrate the compatible operation with suitable water, it is desirable to consider it as 3 to 6% especially 1 to 10% to the skin external-preparations whole quantity. At less than 1%, if quantity of water cannot expect a compatible operation and exceeds 10%, it will cause separation etc. and will cause [ of the system of skin external preparations ] destabilization.

[0011] As plasticizers blended with the skin external preparations of this invention, especially if pliability can be given to a film, it will not be limited, but ester of ester of polybasic acid, the polyalcohol, or the polyalcohol is suitable. As these plasticizers, adipic acid diisopropyl, the sebacic acid diethyl, diethyl phthalate, triethyl citrate, glycerin, propylene glycol, 1,3-butanediol, glycercyl mono-olate, etc. can be illustrated. Among these, it is desirable to use adipic acid diisopropyl, the sebacic acid diethyl, diethyl phthalate, and triethyl citrate especially.

[0012] It is suitable for the loadings of these plasticizers to a film formation agent 2.2-5, and that it is [ as opposed to / especially / 2.3-3, therefore the skin external-preparations

whole quantity ] 8 to 13.5% especially 2.2 to 25% at a bulk density. Since it becomes the film which is rigid in plasticizers being less than 2.2 times the amount of a dermatoplasty agent, if it becomes easy to exfoliate from the skin and exceeds 5 times the amount, about [ checking film formation ], separation, etc. will be caused and it will become the cause of destabilization of the system of skin external preparations.

[0013] As an antifungal in the skin external preparations of this invention Clotrimazole, miconazole nitrate, econazole nitrate, isoconazole nitrate, a pyrrole nit phosphorus, the tolnaftate, BIFUMASHIN, a trichomycin, a cyclo PIROKUSUOKU lamin, exalamide, the haloprogenin, etc. are used suitably. These may use one sort independently or may use it combining two or more sorts. Although the loadings of this antifungal take safety and an antifungal action into consideration and are decided by the kind of antifungal, its thing of the skin external-preparations whole quantity especially considered as 0.8 to 1.5% 0.1 to 5% is desirable.

[0014] The alcohol blended with the skin external preparations of this invention is alcohol which has low chain length's alkyl group, and alcohol of the carbon numbers 1-4 of methanol, ethanol, normal propanol, isopropanol, a normal butanol, t-butyl alcohol, etc. can specifically be illustrated. Even if these are independent, two or more sorts can be mixed, and they can also use one sort, but it is desirable to use especially ethanol and/or isopropanol from a viewpoint of safety and skin penetration nature, and it is most suitable to use ethanol independently. Especially the loadings of alcohol have the desirable thing of the skin external-preparations whole quantity considered as 60 to 80% 50 to 95%. Since a film formation agent does not fully dissolve at less than 50% in loadings, when there is un-arranging -- the perviousness to the horny layer of a medicine

worsens -- and loadings exceed 90%, the flexibility of other ingredients will be restricted too much.

[0015] [ especially a desirable ingredient and its content ratio ] as skin external preparations of this invention 1 to 4% of the ethylcellulose especially as a film formation agent 2.9 to 4%, and 0.1 to 1% of a methacrylic acid methacrylic acid methyl copolymer, Especially, it is 0.8 to 1.5% as an antifungal, and 50 to 95% of ethanol is [ 1 to 10% of water / 2.5 to 25% of plasticizers / 0.1 to 2% of clotrimazole ] 60 to 80% as alcohol 8 to 13.5% 3 to 6% especially 0.4 to 0.8%.

[0016] The optional component used with the usual skin external preparations in addition to these essential ingredients can be blended with the skin external preparations of this invention in the range which does not spoil the effect of this invention. As an optional component, anti-oxidants, such as ultraviolet ray absorbents, such as preservatives, such as a pH adjuster, a surface-active agent, a thickener, methylparaben, and butylparaben, a benzophenone inductor, and an aminobenzoic acid inductor, gamma-tocopherol, and BHT, spice, etc. are mentioned, for example. Furthermore, the ingredient which eases or treats accompanying condition, such as inflammation accompanying dermatomycosis, such as anti-inflammatory agents, such as antipruritic agents, such as antihistamines, such as diphenhydramine, and crotamiton, and glycyrrhetic acid, and a local anesthetic, can also be blended. In order to manufacture the skin external preparations of this invention from these essential ingredients and optional components, the procedure of cooling is [ that what is necessary is just to carry out using the usual procedure ] employable, after carrying out weighing of these ingredients, carrying out heating churning and making it dissolve.

[0017]

[Example] Although a work example is given and this invention is explained in more detail hereafter, it cannot be overemphasized that this invention is not limited to these work examples.

[0018] Carried out weighing of the ingredient shown in one to work-examples 1-3 and comparative example 3 table 1, and carry out heating churning, it was made to dissolve in 80 degrees C, and the skin external preparations of work examples 1-3 and comparative examples 1-3 were obtained by cooling. After applying these to a bottom arm, it rubbed with the absorbent gauze made to become wet with water, and the detachability from the skin was evaluated in accordance with the following standard. A result is shown in Table 1.

- : it is hard to exfoliate.

+ : it is easy to exfoliate.

++ : it is very easy to exfoliate.

Table 1 shows that the skin external preparations of this invention which blended two or more sorts of film formation agents have the outstanding exfoliation resistance.

[0019]

[Table 1]

成 分 (%)	実施例 1	実施例 2	実施例 3	比較例 1	比較例 2	比較例 3
アジピン酸ジイソプロピル	11	11	5	11	5	11
エチルセルロース	4.5	3.5	0.5	5	1	0
メタアクリル酸メタアクリル酸 メチルコポリマー	0.5	0.5	0.5	0	0	5
クロトリマゾール	3	1	0.5	3	0.5	3
ジフェンヒドラミン	0.5	0.5	0.5	0.5	0.5	0.5
水	4	4	4	4	4	4
エタノール	76.5	79.5	89	76.5	89	73.5
剝離試験	—	—	—	+	++	++

[0020] Weighing of the ingredient shown in four to work-examples 4-7 and comparative example 5 table 2 was carried out, and the skin external preparations of work examples 4-7 and comparative examples 4-5 were obtained like work examples 1-3. When these clarity and colors of solution were observed visually, all were a little cloudy, and the skin external preparations of the comparative examples 4-5 which do not contain water had a problem in homogeneity, but each skin external preparations of work examples 4-7 were water-white, and excellent in homogeneity. A result is shown in Table 2.

[0021]

[Table 2]

成 分 (%)	実施例 4	実施例 5	実施例 6	実施例 7	比較例 4	比較例 5
アジピン酸ジイソプロピル	15	10	5	11	11	11
エチルセルロース	4.5	3.5	0.5	4.5	1	4
メタアクリル酸メタアクリル酸 メチルコポリマー	0.5	0.5	0.5	0.5	4	1
クロトリマゾール	3	1	0.5	3	0.5	3
ジフェンヒドラミン	0.5	0.5	0.5	0.5	0.5	0.5
水	10	5	1	1	0	0
エタノール	66.5	79.5	92	79.5	83	80.5
溶状	無色透明	無色透明	無色透明	無色透明	やや白濁	やや白濁

[0022] Weighing of the ingredient shown in eight to work-example 12 table 3 was carried out, and the skin external preparations of work examples 8-12 were obtained like work examples 1-3. Detachability was collectively evaluated like work examples 1-3. A result is shown in Table 3. Table 3 shows not checking the effect of this invention, even if it uses which plasticizers shown in Table 3.

[0023]

[Table 3]

成 分 (%)	実施例 8	実施例 9	実施例 10	実施例 11	実施例 12
エチルセルロース	3.5	3.5	3.5	3.5	3.5
メタアクリル酸メタアクリル酸 メチルコポリマー	0.5	0.5	0.5	0.5	0.5
クロトリマゾール	1	1	1	1	1
ジフェニヒドラミン	0.5	0.5	0.5	0.5	0.5
グリチルレチン酸	0.5	0.5	0.5	0.5	0.5
クエン酸	0.1	0.1	0.1	0.1	0.1
水	4	4	4	4	4
エタノール	80	80	80	80	80
アジピン酸ジイソプロピル	9	0	0	0	0
セバシン酸ジエチル	0	9	0	0	0
フタル酸ジエチル	0	0	9	0	0
グリセリルモノオレート	0	0	0	9	0
クエン酸トリエチル	0	0	0	0	9
剥離試験	—	—	—	—	—

[0024] About the skin external preparations obtained in work-example 13 comparative example 1 and the work example 8, the medicine reservoir sex test in a horny layer which used the guinea pig was done. Namely, the Hartley system white kind guinea pig (maleness, 300-350g) which carried out the closed patch of 0.1ml of the specimens is slaughtered for every fixed time. Exfoliate, pierce the regions-of-back skin by punch in a

circle 30mm in diameter, it is immersed into 30ml of methanol, and ultrasonic waves are applied for 3 minutes. It was immersed after that for 24 hours, and after applying to ultrasonic waves for 3 minutes again and extracting, a fixed quantity of quantity of the clotrimazole which carries out a scalpel rise to a volumetric flask at 50ml of wash lumps and which is stored by HPLC was carried out. A result is shown in Table 4. the skin external preparations of Table 4 to the work example 8 -- an antifungal -- the inside of a horny layer -- high concentration -- and making it store for a long time understands.

[0025]

[Table 4]

サンプル	スタート時 ( $\mu\text{g}/\text{site}$ )	9時間後 ( $\mu\text{g}/\text{site}$ )	24時間後 ( $\mu\text{g}/\text{site}$ )
実施例 8	0	3 0	5 0
比較例 1	0	7	1 3

[0026]

[Effect of the Invention] the skin external preparations of this invention -- an antifungal -- high concentration -- and since it can be made to store in a horny layer, it is very useful for the treatment of a mycosis for a long time, i.e., very efficiently.

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[Translation done.]